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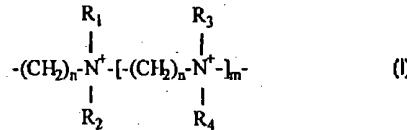
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(71) Applicant (for all designated States except US): SEN-SORMETRIX INTERNATIONAL LIMITED [-]; Caribbean Corporate Services Limited, Omar Hodge Building, Wickhams Clay 1, P.O. Box 362, Road Town, Tortola (VG).		
(72) Inventors; and		Published
(75) Inventors/Applicants (for US only): ALBADRAN, Jafar [JQ/GB]; City Technology Limited, Walton Road, Portsmouth PO6 1SZ (GB). McMURRAY, Neil, Hamilton [GB/GB]; Department of Materials Engineering, University of Wales Swansea, Singleton Park, Swansea SA2 8PP (GB).		With international search report.
(74) Agent: GILHOLM, Steve; Harrison Goddard Foote, Belmont House, 20 Wood Lane, Leeds LS6 2AE (GB).		

(54) Title: QUATERNARY AMMONIUM SALTS, POLYMERIC FILM CONTAINING THEM AND COLORIMETRIC DEVICE



(57) Abstract

There is described a polymeric quaternary alkyl ammonium cation of general formula (I), or a salt thereof; in which R₁, R₂, R₃ and R₄, which may be the same or different are each alkyl C₁ to 20; m is an integer from 1 to 100; and n is an integer from 1 to 7. There is also described a film formulation comprising a cation of formula (I), a colorimetric sensor device comprising said film and an endotracheal intubation apparatus comprising a sensor.

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QUATERNARY AMMONIUM SALTS, POLYMERIC FILM CONTAINING THEM AND COLORIMETRIC DEVICE

This invention relates to oligomeric/polymeric quaternary alkyl ammonium cations, and salts thereof, for incorporation in colorimetric film sensors particularly for the
5 detection of carbon dioxide.

Carbon dioxide sensors are known which incorporate quaternary alkyl ammonium salts of pH indicator dye acids and carbonic acid within a thin transparent polymer membrane. They act as rapidly responding, reversible and non-consuming
10 detectors of carbon dioxide in the gas phase. Such sensors respond by changing colour on exposure to carbon dioxide. Furthermore, the response may be made quantitative by monitoring optical absorbance e.g. using monochromatic light. Colour change occurs through the reversible protonation of the indicator dye anion by carbonic acid formed by the reversible reaction of carbon dioxide with water
15 bound within the film. Such sensor films have applications in medicine, horticulture, air conditioning systems, environmental monitoring and industrial health and safety.

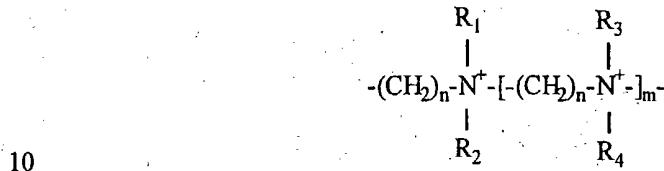
The use of such quaternary alkyl ammonium salts is described in, *inter alia*, US
20 Patent No. 5,005,572, European Patent No. EP 0 509 998 and International Patent
Application No. WO 96/24054.

Known quaternary alkyl ammonium cations, and their salts, tend to be mobile within
a sensor film and can therefore be lost through migration. Migration places
25 significant restriction on the choice of sensor substrate (which must be compatible
with the quaternary alkyl ammonium salt).

Also, known quaternary alkyl ammonium salts are not universally compatible with
organic polymers, further restricting the choice of polymers for sensor film
formulation.

We have now surprisingly found that a high molecular weight oligomeric/polymeric quaternary alkyl ammonium cation, or salts thereof, which are less mobile within a sensor film reducing the extent to which migration can occur. Reduced migration allows a wider choice of substrate materials which may now be thermodynamically compatible with the quaternary ammonium salt.

5 According to the invention we provide a polymeric quaternary alkyl ammonium cations of the general formula I and salts thereof.



in which R_1 , R_2 , R_3 and R_4 , which may be the same or different, are each alkyl C1 to C20;

15 m is an integer from 1 to 100; and

n is an integer from 1 to 7.

By the term polymeric, it is also intended to include oligomeric, R_1 , R_2 , R_3 and R_4 , which may be the same or different, are preferably alkyl C5 to 10.
20 It is preferred that the values of n and m together should have a total in the range of from 4 to 8.

Preferably, m is an integer from 1 to 50, more preferably from 1 to 25, especially 1 to 10 and particularly 1 to 7.

25

Particularly preferred salts are 1,8-octane-di-tripentyl ammonium bromide and 1,8-octane-di-tripentyl ammonium hydroxide.

The salts of the cations of formula I may be selected from the group halide e.g. fluoride, chloride, bromide or iodide; hydroxide; carbonate and tetrafluoroborate. Of the halides, bromide salts are preferred, but especially preferred are the hydroxide salts.

5

These provide increased migration/leaching resistance for the quaternary alkyl ammonium pH indicator dye salts and bicarbonate salts essential for sensor function.

10 The cations of formula I, and thereof, are advantageous in that they produce an improved pH indicator dye with a greater compatibility with polymers, therefore allowing a wider choice of polymers for sensor film formulation.

15 According to a further feature of the invention we provide a film formulation comprising a cation of formula I, or a salt thereof, in intimate mixture with a transparent film-forming polymer vehicle.

20 The transparent film-forming polymer vehicle should be compatible with the indicator material, such that the latter does not exude or otherwise undergo phase separation over a prolonged period (for the intended lifetime of the sensor). Thus, the film-forming polymer should be volatile, e.g. at room temperature and the polymeric quaternary ammonium cation, or a salt thereof, should be soluble in the polymer. The film-forming polymer vehicle should preferably be hydrolytically stable in order to avoid unwanted changes in the pH in the absence of carbon dioxide. The polymer should furthermore be permeable to carbon dioxide.

25

30 The hydrolytically stable film-forming polymer may be water-soluble or organic solvent-soluble. It is preferred that the film-forming polymer is organic solvent soluble. Examples of suitable organic solvent soluble film-forming polymers include polyvinyl butyral, polyvinyl methyl ether, polymethyl ether, polymethyl methacrylate, ethyl cellulose and polystyrene.

Examples of water-soluble film-forming polymers which also have good resistance to hydrolysis include hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol (100% hydrolysed) and polypropylene glycol.

5

Further examples of polymers include polydimethyl silicone, and polyurethane.

According to another feature of the invention we provide a colorimetric sensor device containing one or more of the aforementioned quaternary ammonium salts. Such a 10 device may generally comprise;

- 15 a polymeric quaternary ammonium cation of formula I, or a salt thereof;
- at least one pH sensitive dye; and
- a film-forming polymer.

15

Any conventionally known pH sensitive dyes may be used, including thymol blue, m-cresol purple, xylenol blue and/or cresol-red.

20 The volatile polymer or oligomer may be any such material which is conventionally known in the art, for example, such as is described in PCT patent application No. WO96/24054 which describes that the film forming component is preferably a water-insoluble low volatility organic substance, which is not susceptible to alkaline hydrolysis and is liquid at temperatures below 100°C, e.g. at room temperature, or is semi-solid e.g. of waxy structure, at room temperature.

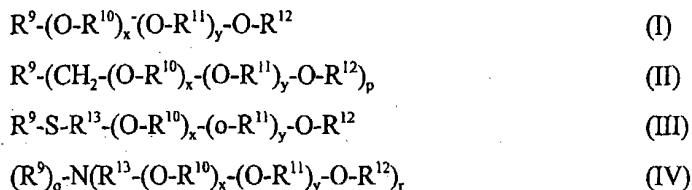
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Compounds which are "susceptible to alkaline hydrolysis" includes compounds such as those containing ester groups which are subjected to alkaline hydrolysis in the presence of a basic component.

30 The film forming component may have a molecular weight (weight average molecular weight = M_w) below 15,000, preferably below 10,000. The film forming

component may be selected from the group consisting of alcohols, phenols and alkoxyated derivatives of such substances, e.g. having at least one linear or branched polyether. The film forming component may have be a compound having one of the following structures:

5



10

wherein R^9 and R^{12} each represents H or a linear or branched hydrocarbon residue of 1 to 50 carbon atoms, optionally containing one or more double bonds, triple bonds and/or ring structures,

15

R^{10} , R^{11} and R^{13} each represents a linear or branched hydrocarbon residue of 1 to 10 carbon atoms,

x and y are equal or different integers from 0 to 100,

p is an integer from 1 to 6, and

q and r are equal or different integers from 0 to 4.

20

Examples of compounds having the above structures (I) to (IV) are the following:

25

Polyalkylene glycols, such as polyethylene glycols, polyethylene glycols, polypropylene glycols, polybutylene glycols and copolymers of ethylene oxide, propylene oxide and/or butylene oxide. Other linear polyethers, such as polytetrahydrofurans. Alkoxyated alcohols or phenols, such as ethoxylated, propoxylated or butoxylated alcohols derived from fatty alcohols (straight or branched, saturated or unsaturated, etc), alkyl phenols, dialkyl phenols, alkyl naphthalenes, bisphenol A, alkyne diols, lanolin, cholesterol, phytosterol, sitosterol, glucose ethers and silicones; and mixed ethoxylated/propoxylated alcohols.

30

Branched polyethers, for instance products obtained by ethoxylating and/or propoxylating trimethylol propane or pentaerythritol. Alkoxyated amines, such as

ethoxylated and/or propoxylated primary or secondary amines or diamines. Alkoxylated (ethoxylated and/or propoxylated) thiols. Dialkyl ethers, e.g. dioctyl ether.

5 Silicone oligomers or polymers may also be used since they have the advantage that, *inter alia*, they are highly permeable to carbon dioxide. For example, a typical silicone polymer has permeability (that is, the gas transmission rate of a film of the polymer of thickness 0.001 inch, expressed as cubic centimetres of gas transmitted through 1 mm of film per 24 hours per square inch of film with one atmosphere differential across the film) is typically as follows:

10 About 100,000 for oxygen and about 500,000 for carbon dioxide (compared with figures of respectively about 1,000 and 5,000 for PTFE; 500 and 2,000 for low density polyethylene; 100 and 500 for cellulose acetate; and 1 and 1

15 for polyvinylidene chloride).

20 The silicone oligomers and polymers are, easy to handle and to apply to a suitable substrate using an organic solvent such as a hydrocarbon type solvent (such as hexane), a chlorinated solvent (for example, chloroform or dichloromethane), an ether solvent (such as tetrahydrofuran), or a low molecular weight oligomeric silicone (such as a cyclic dimethyl silicone).

25 Because the silicone oligomers or polymers are substantially non-curable they have good storage stability and can be stored indefinitely in the solvent.

30 The silicone oligomers or polymers are also readily compatible with the pH sensitive dye and the basic substance, and can be applied in the form of a film on a preformed substrate (such as a plastics, paper or glass substrate). Alternatively, the silicone may be applied as an impregnation throughout a porous carrier medium, for example, of glass fibre, paper, plastics, textile fabric or the like. It is particularly preferred to use

such materials which have been provided with a hydrophobic surface treatment, for example, by silanisation.

The silicone oligomers or polymers are preferably substantially linear and 5 substantially free of hydrophilic groups; preferred substituents for the silicone chain are methyl groups (although other low molecular weight hydrophobic groups may be employed, such as ethyl or trifluoromethyl groups).

It is particularly preferred that the silicone oligomer or polymer is a linear 10 polydimethylsiloxane. The silicone preferably has a molecular weight in the range of 200 to 200000, and is preferably optically transparent. When higher molecular weight silicone polymers are used they are very good binders and have a low glass transition temperature such that they maintain their physical properties over a wide range of temperatures. They are furthermore non-toxic and non-volatile, and 15 hydrolytically stable.

The silicone oligomers or polymers are furthermore compatible with the indicator ingredients (the dye and the basic substrate), and can be free of migratable low molecular weight materials such as plasticisers or the like.

20

Preferably the device will be in the form of film sensor and the film may therefore require a support such as a polypropylene proper sheet, a cellulose layer or a plastics foil material. However, the sensor of the invention preferably comprises a silanised 25 paper support which is preferably non-translucent i.e. is reflective, such as a white film which aids in visual indication. Alternatively the support may be a transparent film on a glass substrate which permits quantitative interrogation with e.g. monochromatic light.

30 The sensor device of the invention functions by the reaction of carbon dioxide with traces of water bound within the sensor film to form carbonic acid (H_2CO_3). Thus,

dissociation of H_2CO_3 to H^+ and HCO_3^- produces a fall in sensor pH which in turn produces an optical absorbance change through the reversible protonation of the pH indicator dye.

5 Thus, according to a further feature of the invention we provide a method of carbon dioxide detection which comprises placing a sensor according to the invention *in situ* and observing a colour change.

10 The sensors of the invention have particular utility in determining the proper placement of a tracheal tube of an endotracheal intubation device in a patient.

Thus, a further feature of the invention is to provide an endotracheal apparatus comprising a sensor as hereinbefore described.

15 We further provide a method for determining the proper placement of an endotracheal tube which comprises inserting an endotracheal tube comprising a sensor according to the invention, into a patient and observing a colour change.

20 The invention will now be described, but in no way limited by the following examples.

Example 1

Preparation of 1,8 Octane-di-tripentyl Ammonium Bromide

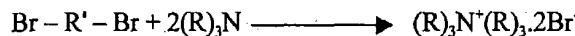
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Chemicals

- Tri Pentyl Amine (TPA) 97%, fw: 227.44, bP: 81-83°C, d: 0.788.
- 1,8-Dibromoocetane (DBO) 98%, fw: 286.06, bp: 270-272°C, d: 1.477.
- 30 • Methanol, d: 0.791.

Experimental and Results

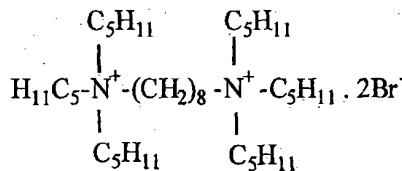
The reactants DBO and TPA were mixed in a 1:2 molar ratio plus an excess of 50% of TPA. Thus, 5g of DBO, 13g of TPA and 18g of methanol were refluxed together 5 at 68°C for 64 hours. Methanol and excess amine were removed under vacuum at 70°C using a rotary evaporator. The result was a biphasic liquid which rapidly separated into two layers. The top layer was a colourless liquid (code name DC-2L0 which can easily be poured off from the bottom thick oily layer (code name DC-2S were examined by mass spectrometry. The results obtained using electro-spray mass 10 spectroscopy showed that DC-2S contained the target molecule octane-1,8-di-tripentyl ammonium bromide formed through the reaction:



15 R is C₅H₁₁ R' is C₈H₁₆

The new doubly charged dimeric tetraalkyl ammonium salt Octane-1,8-di-tripentyl Ammonium Bromide (OTAB) has a formula weight of 726.91. The chemical structure of OTAB is shown below:

20



25

1,8-Octane-di-Tripentyl Ammonium Bromide (OTAB)

C₃₈H₈₂NBr₂, f.w: 726.91

5 **Example 2**

Carbon dioxide Film Sensor using OTAB

3.63g of OTAB was dissolved in 12g (15.2mL) of methanol. 4g of Ag₂O was added
10 to the solution and stirred for four hours. The resulting 20% w/w methanolic
solution of the hydroxide salt 1,8-Octane-di-tripentyl ammonium hydroxide
(OTAOH) was collected by decantation.

0.1g of the pH indicator dye (m-cresol purple, thymol blue or xylanol blue) was
15 dissolved in 10g of the 20% w/w OTAOH methanolic solution. Methanol was
evaporated using a rotary evaporator and 7.9g of tetrahydrofuran was added to form a
20:1% base:dye solution.

0.3g of the base:dye solution was added to 10g of 3% w/w polydimethyl silicone
20 (PDMS) polymer solution and mixed before applying to a 1PS filter paper.

Filter papers loaded with the sensor materials above showed a good response to 5%
carbon dioxide and it is limited by the pH operating range of the dye. Adding a small
amount (0.5-20 parts per hundred parts polydimethyl silicone) of polyethylene glycol
25 (PEG) was again found to increase both the equilibrated sensitivity to CO₂ and the
sensor response rate.

Samples with the above formulation were prepared with a loading of 20 phr of
OTAOH, 1 phr of m-cresol purple and 2 drops of PEG (~18 phr).

Example 3**Film behaviour under Long Term Exposure to Carbon dioxide**

5 A fresh base:dye solution has been prepared using the conventional "two pot" formulation. 01g of m-cresol purple pH indicator dye was dissolved in 10g of 10% w/w methanolic solution of tetraoctyl ammonium hydroxide (TOAOH). The methanol was replaced by tetrahydrofuran by evaporating the methanol and adding 8.9g of tetrahydrofuran 0.36g of the above base:dye solution was added to 10g of
10 10% w/w polymer solution (PDMS in dichloromethane) along with 0.36g of 0.5% w/w PEG before casting on microscope glass slide.

The film was stored in an airtight glass jar with PURAFIL 100% carbon dioxide was passed into the jar to transform the film to the acidic state (yellow). The film was
15 flushed with air after 24, 48, 96 and 800 hours and found to change colour to blue. The above result proved that exposing the film sensor to 100% carbon dioxide does not destroy the film mechanism provided that the film is well protected from other acid gases.

20 **Example 4**

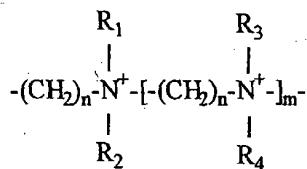
The Film Shelf Life Test

Two film sensors were prepared in a similar fashion to the one described in the
25 previous example. One of the above films was prepared without the addition of PEG. Both films were stored in an airtight glass jar with some PURAFIL for eighteen months. The films did not show any colour change.

CLAIMS

1. A polymeric quaternary alkyl ammonium cation of the general formula I, or a salt thereof;

5



in which R_1 , R_2 , R_3 and R_4 , which may be the same or different, are each alkyl C1 to C20;

10 m is an integer from 1 to 100; and
 n is an integer from 1 to 7.

15 2. A polymeric quaternary alkyl ammonium cation according to Claim 1 characterised in that R_1 , R_2 , R_3 and R_4 , which may be the same or different, are each alkyl C5 to 10.

20 3. A polymeric quaternary alkyl ammonium salt according to Claim 1 characterised in that the anions of the salts are selected from the group halide, hydroxide, carbonate and tetrafluoroborate.

4. A polymeric quaternary alkyl ammonium salt according to Claim 3 characterised in that the halide is selected from fluoride, chloride, bromide or iodide.

25 5. A polymeric quaternary alkyl ammonium salt according to Claim 4 characterised in that the halide is bromide.

6. A polymeric quaternary alkyl ammonium salt according to Claim 3 characterised in that the anion is hydroxide.

7. A polymeric quaternary alkyl ammonium salt according to Claim 5 characterised in that the compound is 1,8-octane-di-tripentyl ammonium bromide.
- 5 8. A polymeric quaternary alkyl ammonium salt according to Claim 6 characterised in that the compound is 1,8-octane-di-tripentyl ammonium hydroxide.
9. A film formulation comprising a cation, or a salt thereof according to Claim 1, in intimate mixture with a transparent film-forming polymer vehicle.
- 10 10. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is compatible with the indicator material, such that the latter does not exude or otherwise undergo phase separation over a prolonged period.
- 15 11. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is hydrolytically stable.
12. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is permeable to carbon dioxide.
- 20 13. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is organic solvent-soluble.
- 25 14. A film formulation according to Claim 13 characterised in that the transparent film-forming polymer vehicle is selected from polyvinyl butyral, polyvinyl methyl ether, polymethyl methacrylate, ethyl cellulose and polystyrene.
15. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is water soluble.

16. A film formulation according to Claim 15 characterised in that the transparent film-forming polymer vehicle is selected from hydroxypropyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol (100% hydrolysed) and polypropylene glycol.

5

17. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is a polyurethane.

18. A film formulation according to Claim 9 characterised in that the transparent film-forming polymer vehicle is a silicone oligomer or polymer.

19. A film formulation according to Claim 18 characterised in that the silicone oligomer or polymer is a polydimethyl silicone

15 20. A colorimetric sensor device comprising;

a polymeric quaternary ammonium cation, or a salt thereof, according to Claim 1

at least one pH sensitive dye; and

20 a polymer in which the polymeric quaternary ammonium cation, or a salt thereof, is soluble.

21. A colorimetric sensor device according to Claim 20 characterised in that the pH sensitive dye is selected from thymol blue, m-cresol purple, xylenol blue and 25 cresol-red.

22. A colorimetric sensor device according to Claim 20 characterised in that the polymer is described in PCT patent application no. WO96/24054.

30 23. A colorimetric sensor device according to Claim 20 characterised in that the device is in the form of film sensor and the film is provided with a support.

24. A colorimetric sensor device according to Claim 23 characterised in that the support comprises a material selected from polypropylene sheet, a cellulose layer or a plastics foil material.

5

25. A colorimetric sensor device according to Claim 23 characterised in that the support comprises a silanised paper.

26. A colorimetric sensor device according to Claim 23 characterised in that the support comprises a glass substrate.

27. A method of carbon dioxide detection which comprises placing a sensor according to claim 20 *in situ* and observing a colour change.

15 28. An endotracheal intubation apparatus comprising a colorimetric sensor device according to Claim 20.

20 29. A method for determining the proper placement of an endotracheal tube which comprises inserting an endotracheal tube comprising a colorimetric sensor device according to Claim 20 into the trachea of a patient and observing a colour change.

30. A colorimetric sensor device substantially as described with reference to the accompanying examples.

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INTERNATIONAL SEARCH REPORT

Inte	ional Application No
PCT/GB 99/02081	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07C211/63 G01N31/22 A61M16/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07C G01N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 13, 30 November 1998 (1998-11-30) & JP 10 208543 A (TDK CORP), 7 August 1998 (1998-08-07) abstract	1-5, 9-21, 26, 27
X	EP 0 666 277 A (GEN ELECTRIC) 9 August 1995 (1995-08-09) the whole document	1-6
X	DE 22 03 229 A (HUNT CHEM CORP PHILIP A) 26 July 1973 (1973-07-26) claim 1	1,2
X	DE 19 08 980 A (TH. GOLDSCHMIDT AG) 3 September 1970 (1970-09-03) claim 1	1-5
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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04/11/1999

Name and mailing address of the ISA
 European Patent Office, P.B. 5618 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
 Fax: (+31-70) 340-3016

Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 855 116 C (CIBA AG) 10 November 1952 (1952-11-10) claim 1 ----	1-5
X	DE 905 371 C (MAY & BAKER LIMITED) 1 March 1954 (1954-03-01) page 2 ----	1-5
X	DE 29 05 373 A (GAMBAR LABOR) 6 September 1979 (1979-09-06) claim 1 ----	1-5
X	DE 19 26 436 A (E. R. SQUIBB & SONS INC.) 29 January 1970 (1970-01-29) claims 1-3 ----	1-5
A	WO 96 24054 A (ICOR AB) 8 August 1996 (1996-08-08) cited in the application the whole document ----	1,9-27, 30
A	WO 91 05252 A (ABBEY BIOSYSTEMS LTD) 18 April 1991 (1991-04-18) the whole document & EP 0 509 998 A cited in the application ----	1,9-27, 30
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INTERNATIONAL SEARCH REPORT

national application No.

PCT/GB 99/02081

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 29 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.: 1-6 partly because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6 partly

Present claims 1-6 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) of claim 1 wherein m is an integer from 1 to 7 according to page 2, line 24 of the description. It is stressed that the incomplete search has revealed a very large number of novelty destroying compounds (merely thousand).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No

PCT/GB 99/02081

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